
Directed differentiation of human embryonic stem cells into corticofugal neurons uncovers heterogeneous fezf2-expressing subpopulations.

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Public Summary:

Understanding how neuronal diversity is achieved within the cerebral cortex remains a major challenge in neuroscience. The human embryonic stem cells (hESCs) provide a unique opportunity to study human brain development in a petri dish and to identify the mechanisms that promote the generations of different types of human brain neurons. The gene *Fezf2* is necessary and sufficient for the generation of corticospinal motor neurons in mouse. However, its function during human brain development is poorly understood. This study reports the differentiation of a hFezf2-YFP hESC reporter line into corticospinal motor neurons capable of extending axons toward the spinal cord upon transplantation into neonatal mouse brains. Additionally, we show that triple inhibition of the TGFβ/BMP/Wnt-Shh pathway promotes the generation of hFezf2-expressing cells. Finally, this study unveils the isolation of two novel and distinct populations of hFezf2-YFP expressing cells reminiscent of the distinct *Fezf2*-expressing neuronal subtypes in the developing mouse brain. Overall our data suggest that the directed differentiation of hESCs into corticofugal neurons provides a useful model to identify the molecular mechanisms regulating human brain neuron differentiation and survival.

Scientific Abstract:

Understanding how neuronal diversity is achieved within the cerebral cortex remains a major challenge in neuroscience. The advent of human embryonic stem cells (hESCs) as a model system provides a unique opportunity to study human corticogenesis in vitro and to identify the mechanisms that promote neuronal differentiation to achieve neuronal diversity in human brain. The transcription factor *Fezf2* is necessary and sufficient for the specification of subcerebral projection neurons in mouse. However, its function during human corticogenesis is poorly understood. This study reports the differentiation of a hFezf2-YFP hESC reporter line into corticofugal projection neurons capable of extending axons toward the spinal cord upon transplantation into neonatal mouse brains. Additionally, we show that triple inhibition of the TGFβs/BMP/Wnt-Shh pathway promotes the generation of hFezf2-expressing cells in vitro. Finally, this study unveils the isolation of two novel and distinct populations of hFezf2-YFP expressing cells reminiscent of the distinct *Fezf2*-expressing neuronal subtypes in the developing mouse brain. Overall our data suggest that the directed differentiation of hESCs into corticofugal neurons provides a useful model to identify the molecular mechanisms regulating human corticofugal differentiation and survival.

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